REMARKS/ARGUMENTS

Claims 22-60 are active.

Claims 22-37 track the subject matter in prior claim 1 and include products (recombinant adenovirus), compositions and methods of using. Support for these claims may be found in the original claims and specification as follows: claim 22 (claim 2, [0027], [0034]), claims 23-24 ([0004][0008-0009], [0038], [0060]), claim 25 (claim 3, [0028], claim 26 (claim 4), claim 27 (claim 5), claim 28 (claim 6), claims 29-30 (claim 7), and claims 31-36 (claims 10-15, [0068-0072]) and claim 37 (claim 21).

Claims 38-51 track the subject matter in prior claim 2 and include products (recombinant adenovirus), compositions and methods of using. Support for these claims may be found in the original claims and specification as follows: claim 38 (claim 2, [0023, 0027, 0029, 0034]), claims 39-40 ([0004][0008-0009], [0038], [0060]), claims 41-42 (claims 5-6), claims 43-44 (claim 7), and claims 45-50 (claims 10-15, [0068-0072]) and claim 51 (claim 21). Claims 52-55 track prior claims 8-9 and refer to nucleic acid product. Claims 56-60 track prior claims 16-20 and refer to a method for making a recombinant adenovirus. Thus, as evident from above, no new matter has been introduced.

The use of the expression "replicating adenovirus" for designating the starting material from which the adenovirus of the invention are obtained, indicates which portions of the adenoviral genome must be present in this starting material. Typically, replicating adenoviruses are either wild-type adenoviruses, or modified adenoviruses which comprise almost all the sequences of the wild-type adenoviral genome, with the exception of E3 which is not essential for replication, and which may thus optionally be deleted or not (cf. "First generation vectors" pages 2-3 in the enclosed publication of GRAHAM, which also provides in Figure 1b a map of the adenoviral genome). It is to be noted that the adenoviruses which are deleted in E1 are not "replicating adenoviruses", since they cannot replicate in cells

permissive for the corresponding wild-type adenovirus, but only in cells wherein the deficient E1 function is complemented in trans (by use of a helper virus or a transformed cell expressing E1). The claims now specify the metes and bounds of the deletion and clearly indicate the region of the adenovirus genome which may be deleted in part (i.e., the region comprised between the end of the left ITR and the beginning of the sequence encoding E1A, which implies that the recombinant adenoviruses resulting from the deletion always keep the full length left ITR, and also the full-length E1 coding region), and further they indicate those of the functional elements (namely the encapsidation signals) present in this region which should be deleted, and those which should not be deleted.

The Applicants thank Examiner Makar and Sullivan for the helpful and courteous interview of June 22, 2007. To address the rejections under 35 U.S.C. §112, it was suggested that the claim language be comprehensively revised to refer to which viral elements are present or not present in the recombinant adenoviruses. To address possible prior art issues, it was suggested that the Applicants discuss why the particular modifications to the claimed adenoviruses provide a novel and unobvious construct.

Objection—Oath/Declaration

The Applicants thank Examiner Makar for indicating by telephone on August 27, 2007 that this objection will be withdrawn since the oath signed by the inventors has a side-by-side translation of its content in both French (left side) and English (right side).

Objection—Claims

Claims 7-15 and 20-21 were objected to as being improperly multiply dependent. This objection is now moot.

Objection—Abstract

This objection to the Abstract is moot in view of the attached replacement Abstract.

Rejection—35 U.S.C. §112, first paragraph

Claims 1-6 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description. This rejection is moot in view of the amendments above.

Rejection—35 U.S.C. §112, second paragraph

Claims 1, 2, 16 and 18 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is moot in view of the amendments above.

Rejection—35 U.S.C. §102(b)

Claims 1, 3-6 and 16-19 were rejected under 35 U.S.C. 102(b) as being anticipated by Soudais, et al., Molec. Ther. 3:631. This rejection is moot in view of the cancellation of the prior claims. It does not apply to the new claims because Soudais does not disclose all the elements required by the recombinant adenovirus of claim 22 or the recombinant pseudoreplicating adenovirus of claim 38.

Soudais report the characterization of the cis-acting sequences involved in canine adenovirus packaging, *viz.* (*videlicit*, "namely") the encapsidation signals.

Soudais identified the encapsidation signals A_I to A_{XII} by analysis of the sequence of the first 500bp of the genome (see Figure 1), and then generated several mutants with different combinations of deletions of these encapsidation signals. These mutants are listed and represented in Figure 2b. These mutants were generated by recombination between the CAV genome and transfer plasmids which were themselves derived from the plasmid

pCAVGFP (see "Construction of packaging mutants", page 632, 2nd column). The plasmid pCAVGFP contains the CAV-2 ITR and packaging domain from bp 1 to 411, followed by a 1.9-kb EGFP expression cassette, and by the CAV-2 E2B region. This means that this plasmid does not comprise the E1 region. As a consequence, the recombinant viruses obtained from this plasmid do not comprise the E1 region. This is further indicated by page 632, 2nd col., lines 43-44 which specify that "All the vectors in this study are replication-defective as the E1 region is functionally deleted" (page 632, 2nd column, lines 43-44).

This also shown clearly in Figure 2b, which shows that in all the vectors the E1 coding region of CAV-2 (represented at the top of Figure 2b) beginning at position 500, is absent and replaced by the GFP cassette.

In contrast, the vectors of instant Claims 22 and 38 have a deletion which, at most, ends before the beginning of the sequence encoding E1A. They always comprise the full length E1 coding region. Accordingly, Soudais et al. do not anticipate the recombinant adenoviruses of Claims 22 and 38.

Further, in regard to Claim 22, it is also to be noted that although Soudais describe a recombinant adenovirus which comprises all the A_I to A_{XII} encapsidation signals (CAVGFP-1), this document does not describe any adenovirus wherein a sequence comprised between positions 311-319 (which is situated within the region separating encapsidation signals A_{IX} and A_X--see Figure 1 of Soudais) has been deleted.

In regard to Claim 38, it is to be noted that Soudais does not describe any adenovirus having a deletion comprising the encapsidation signals A_X to A_{XII}, and that does not comprise the A_I to A_{IX} encapsidation signals. Only the vector CAV-GFP-4Δ5 has a deletion which comprises the encapsidation signals A_X to A_{XII}; however, this deletion also comprises the encapsidation signal A_{IX} required by claim 38.

Further, based on Soudais, one of ordinary skill in the art seeking to obtain a recombinant adenovirus able to replicate but unable to produce infectious particles as required by claim 38 would not have been motivated to delete the encapsidation signals A_X to A_{XII} while keeping the encapsidation signals A_I to A_{IX}. Indeed, Soudais reports that the recombinant adenoviruses wherein only the encapsidation signals A_{XI} and A_{XII} are deleted (CAVGFP-2 and CAVGFP-4.8), as well as the recombinant virus wherein the encapsidation signals A_{IX} to A_{XII} are deleted (CAV-GFP-4△5) produce when propagated alone, the same quantity of infectious particles as an adenoviral vector (such as CAVβgal) having a fully functional packaging domain. It is only when it is used in competition with CAVβgal that the CAV-GFP-4△5 produces a lower quantity of infectious particles. In comparison, the recombinant adenoviruses CAVGFP-4.22 and CAVGFP-4.19 (which, in addition to the deletion of the A_{XI} and A_{XII} have respectively a deletion of the encapsidation signals A_{VI} and A_{VII} and A_{II}, A_{III}, A_{VI} and A_{VII}) produce respectively a eight to sixteen-fold lower quantity of infectious particles when propagated alone, (see "Packaging Competition Assay", pages 636-637, Figure 2b, columns "Reduction yield" and "Reduction coinfection", and Figure 4).

From Soudais one of ordinary skill in the art would have concluded from these results that, in order to prevent efficiently the production of infectious particles, the A_{II}, A_{III}, A_{VI} and A_{VII} encapsidation signals must be deleted. Therefore, Soudais does not suggest or provide a reasonable expectation of success for the adenovirus of the present invention where only encapsidation signals A_X to A_{XII} are deleted. Accordingly, the Applicants respectfully submit that this rejection would not apply to the new claims.

Rejection—35 U.S.C. §102(b)

Claims 16-19 were rejected under 35 U.S.C. 102(b) as being anticipated by Crouzet, et al., PNAS. 94:1414. This rejection is moot in view of the cancellation of the prior claims.

It does not apply to the new method of making claims 56-60, because Crouzet does not disclose all the steps required by these claims.

The method of the invention requires recombination in the prokaryotic host that is performed between a previously linearized DNA fragment (donor molecule) comprising the heterologous sequence of interest, and a plasmid comprising the genome of an adenovirus (which can be previously linearized or not). However, in the method of Crouzet, all the recombination steps performed in *E. coli* involve circular DNA molecules (schematized as ovals in Figure 1).

While the Official Action asserts that Crouzet discloses a two-step gene replacement procedure for the generation of infectious adenovirus genomes in *E. coli*, and that "all of the vectors are linearized at some point for manipulation, using a variety of restriction sites at different points of insertion – thus at least one previously linearized outside of an insertion site", this interpretation of the teaching of Crouzet et al. is erroneous. As shown in Figure 1 of Crouzet, all the recombination steps performed in *E. coli* involve circular DNA molecules (schematized as ovals in Figure 1). The linearization is performed by Pad digestion only after recombination, in order to excise the recombinant adenovirus genome flanked by Pad restriction sites (denoted by "P" in Figure 1) from the construct resulting from recombination. Accordingly, this rejection would not apply to the present claims.

Conclusion

This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

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